Temporal and spatial changes of BOLD signal, CBF and CBV in the activated human visual cortex during mild hypoxia

Felipe Rodrigues Barreto[1], Silvia Mangia[2], and Carlos Ernesto Garrido Salmon[3]

[1]*Department of Physics, University of Sao Paulo, RIbeirao Preto, SP, Brazil,* [2]*Department of Radiology, CMRR, University of Minnesota, MN, United States,* [3]*Department of Physics, University of Sao Paulo, Ribeirao Preto, SP, Brazil*

Target audience: neuroscientists interested in functional neuroimaging experiments and human brain physiology.

Purpose. A tight coupling between oxygen consumption and oxygen delivery through the vascular system is essential to proper brain function. Oxygen deprivation through short periods of time is frequent in chronic disorders such as obstructive sleep apnea, which affects 2 to 4% of adult population, and has been suggested to be a risk factor for morbidities such as hypertension and stroke.[1-3] Few human brain studies have analyzed how physiological parameters like cerebral blood flow (CBF), cerebral blood volume (CBV) and cerebral metabolic rate of oxygen ($CMRO_2$) are affected by mild hypoxic hypoxia, both at baseline (i.e., in absence of external stimuli) and during increased neuronal activity (i.e., during stimuli).[4-9] However, no studies have attempted to measure CBF and CBV and $CMRO_2$ during the same experimental session. The present study aimed at quantifying the effect of mild hypoxia on stimulus-induced variations in CBF, CBV and $CMRO_2$ as measured by multimodal fMRI, which included Pulsed Arterial Spin Labeling (PASL) fMRI, Vascular Space Occupancy dependent (VASO) fMRI and Blood Oxygenation Level Dependent (BOLD) fMRI.

Methods. Data from 4 healthy adult subjects (2 M, 27.7 ± 3.0 years) were obtained using a 3T scanner. Visual stimulation paradigm consisted of 7 blocks ([*off-on*]x3+*off*) with duration of 32 s each (total duration of 3.7 min). Visual stimulus consisted of a radial black-white checkerboard flickering at 8 Hz. Anatomical images were acquired using MPRAGE with TE/TR = 3.2/7 ms, FA = 8°, spatial resolution 1x1x1 mm^3, 170 slices. Functional images were acquired with EPI readout and positioned in the visual cortex, and had a spatial resolution of 3x3x5 mm^3. BOLD fMRI was acquired with TE/TR= 40/2000 ms and 5 slices; PASL[10] fMRI with TE/TR = 18/2000 ms, post-labeling delay = 1.5 s, label thickness = 200 mm and 3 slices; VASO fMRI with TE/TI/TR = 18/700/2000 ms and 3 slices. Subjects were equipped with a nose clip and breathed a gas mixture of O_2 balanced with high purity N_2 through a mouthpiece. An initial dataset of MPRAGE, BOLD, PASL and VASO images were acquired during the normoxia phase, where oxygen content was adjusted to 21%. During the following hypoxia phase, oxygen content was adjusted to 12%. A 5 min adaptation period was used to have oxygen saturation stabilized in the 80 to 85% range during hypoxia, prior to the acquisition of the second dataset of BOLD, PASL and VASO images. Arterial blood O_2 saturation, partial expired CO_2, heart (HR) and breath rates (BR) were continuously monitored using a vital signs monitor. All images were preprocessed using SPM8, and activated areas were determined using standard GLM. For PASL and VASO images, a first order gamma function was used as regressor. BOLD, PASL and VASO parameters were first averaged within voxels belonging to the overlap of the activated volumes obtained with the various modalities and conditions in each subject, and then compared among conditions. Sizes of activated volumes were also calculated. Finally, stimulus-induced changes in $CMRO_2$ and oxygen extraction fraction (OEF) were estimated using a previously proposed model.[11]

Results and discussion. HR and oxygen saturation changed from 64.6±9.1 bpm and 96.2±0.7% during normoxia to 81.2±7.3 bpm and 79.1±2.3% during hypoxia, respectively ($p<0.01$, paired t-test). No changes in relative expired CO_2, BR or basal CBF were observed during hypoxia as compared to normoxia. In addition, hypoxia did not affect the image SNR. Mean changes in BOLD, CBF, CBV, $CMRO_2$ and OEF in response to visual stimulation in both normoxic and hypoxic conditions are reported in Table 1, whereas mean time courses of BOLD, CBF and CBV during the functional paradigm are shown in Fig. 1. All activated areas shrank during hypoxia relative to normoxia (Fig. 2), by 48.1±37.2%, 24.0±22.1% and 23.4±17.9% for BOLD, PASL and VASO images, respectively. CBV data from two subjects needed to be discarded due to poor data quality. Despite the small number of subjects, robust reductions of BOLD amplitudes and activated volumes were observed in hypoxia as compared to normoxia, in agreement with previous findings.[7] In addition, the BOLD time-course showed a slight reduction in the post-stimulus undershoot during hypoxia. Also in agreement with previous findings,[4,7] the stimulus-induced ΔCBF and ΔCBV were not different between conditions (Table 1), whereas the activated volumes were reduced. No statistically significant differences were observed either for $\Delta CMRO_2$. Task-induced OEF reductions were significantly smaller during hypoxia as compared to hypoxia ($p<0.01$). This finding likely reflects inherent differences in the amount of oxygen available to the tissue as delivered by the less oxygenated (but unchanged) blood flow in presence of unchanged energy demands of the activated region. Subtle changes in CBF, CBV and $CMRO_2$ responses might still occur during hypoxia, however studies on a larger cohort of subjects are warranted to detect such effects.

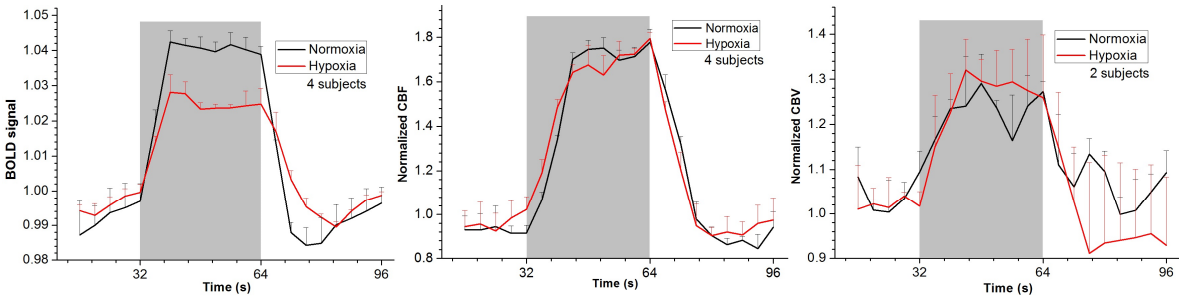

Figure 1. Time courses of BOLD, CBF and CBV averaged across trials and subjects during normoxia and hypoxia. Data shown as mean ± SD.

	ΔBOLD (%)	ΔCBF (%)	ΔCBV (%)	$\Delta CMRO_2$ (%)	ΔOEF (%)
Normoxia	4.0±0.3 **	73.7±5.7	25.2±7.5	34.5±7.5	-22.3±1.9 **
Hypoxia	2.4±0.3	70.9±8.7	28.5±13.8	30.2±11.6	-17.3±1.6

Table 1. Mean changes in BOLD, CBF, CBV, $CMRO_2$ and OEF due to stimulation during normoxia and hypoxia. **: normoxia≠hypoxia ($p<0.03$, unpaired two-tailed t-test).

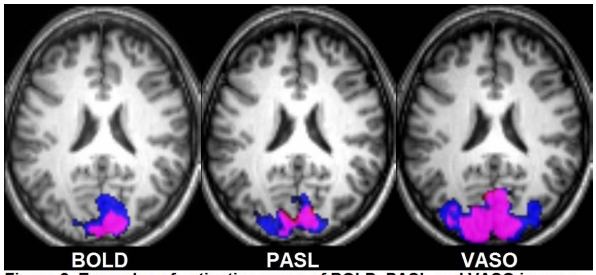

Figure 2. Examples of activation maps of BOLD, PASL and VASO images during normoxia (blue), hypoxia (red) and overlapping areas (pink).

Conclusion. Mild hypoxia during visual stimulation produced substantial reductions in the active volumes detected in BOLD, ASL and VASO images, which might indicate smaller cortex recruitment during hypoxia. The brain regions commonly activated during hypoxia and normoxia had reduced BOLD amplitudes and smaller OEF reductions, but no changes in the amplitude of vascular and $CMRO_2$ responses.

References and Acknowledgements. [1] Nieto et al. JAMA. 2000; 284: 1829-36. [2] Epstein et al. 2009. JCSM; 5: 263-76. [3] Parra et al. 2000. Am J Respir Crit Care Med; 161: 375-80. [4] Tuunanen and Kauppinen, Neuroimage. 2006; 30: 102-9. [5] Tuunanen et al. MRM. 2006; 24: 993-9. [6] Tuunanen et al. JCBFM. 2006; 26: 263-73. [7] Ho et al. Neuroimage. 2008; 41: 179-88. [8] Shen et al. Neuroimage. 2012; 59: 3450-6. [9] Mintun et al. 2001. PNAS; 98: 6859-64. [10] Golay et al. MRM. 2005; 53: 15-21. [11] Uludag et al. NeuroImage. 2004; 23: 148-55. Supported by CAPES and CInAPCEe Program.